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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,300	02/24/2004	Roy A. Black	016761-0171	5048

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/784,300	BLACK ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006 and 22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-27 are pending in the application.

Election/Restriction

[2] Applicant's election of Group II, claims 23-27, in the response filed on 4/18/2006 is acknowledged.

[3] In a telephone conversation with applicant's representative, Mr. Brian McCaslin, on 6/19/2006, Mr. McCaslin queried the examiner regarding change of the elected invention. Mr. McCaslin stated that applicant would like to elect Group I rather than Group II. The examiner acknowledged applicant's request and indicated that the invention of Group I, claims 1-22, would be examined on the merits instead of Group II. Applicant's request is evident in the supplemental response filed on 6/22/2006.

[4] Applicant's election of Group I, claims 1-22, in the response filed on 6/22/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

[5] Claims 23-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/31/2006.

Priority

[6] Applicant's claim for domestic priority under 35 USC § 120 to US non-provisional application 09/244,984, filed on 2/4/1999, now US Patent 6,842,704, is acknowledged. Applicant's claim for domestic priority under 35 USC § 119(e) to US provisional applications 60/117,476, filed on 1/27/1999, 60/135,499, filed on 3/30/1998, and 60/073,709, filed on 2/4/1998, is acknowledged. It is noted that the invention of claims 1-16, 18, and 22 and appear to be supported by the specification of provisional application 60/073,709. The examiner can find no support for the limitations of claims 17 and 19-21 in provisional application 60/073,709 and thus, claims 17 and 19-21 are not given priority to the earliest prior filing date. However, the examiner can find support for claims 17 and 19-21 in provisional application 60/135,499.

[7] Applicant should update the status of application 09/244,984 in the priority claim at the first paragraph of the specification. According to PTO records, application 09/244,984 is not US Patent 6,842,704.

Information Disclosure Statement

[8] With the exception of references A21 and A38, all references cited in the information disclosure statement filed on 7/27/2004 have been considered by the examiner. A copy of Form PTO/SB/08 is attached to the instant Office action. References have not been considered as there is no publication date provided for these references. See 37 CFR 1.98(b)(5).

[9] If the examiner has inadvertently overlooked an IDS that has been filed in the instant application, applicant's cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Sequence Compliance

[10] In order to perfect sequence compliance, applicant is required to submit 1) a statement that the sequence listing paper copy filed on 7/27/2004 is identical to the computer readable form of the sequence listing and 2) an amendment directing entry of the sequence listing paper copy, filed on 7/27/2004, into the application.

[11] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required

by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly p. 22, line 6 and p. 23, line 22.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[12] Claim(s) 2-7, 11-12, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 2-4 recite the limitations "the TACE catalytic domain," "the pro and catalytic domains of TACE," and "the amino acid residues 1-477 of TACE." There is insufficient antecedent basis for these limitations in the claims. Furthermore, it is unclear as to those amino acids of a TACE catalytic domain or pro-domain that are intended as being encompassed by the claims. It is suggested that applicant clarify the meanings of the terms "TACE catalytic domain" and "the pro and catalytic domains of TACE."

[b] Claims 4-5 are indefinite in the recitation of "amino acid residues 1-477 of TACE" (claim 4), "amino acid residue Serr266," and "amino acid residue Asn542" (claim 5) as there is no recited reference sequence such that a skilled artisan can ascertain the desired amino acid(s) to which the claims refer. It is suggested that, for example, applicant refer to a reference sequence by use of a sequence identifier.

[c] Claims 6-7 are indefinite in the recitation of "binding partner suitable for co-crystallization" as it is unclear as to the criteria used to determine whether the binding partner is considered to be "suitable" or unsuitable for co-crystallization. For example, is the term "suitable" meant to modify the scope of binding partners to encompass only those having a certain binding affinity for the TACE polypeptide? Or, for example, is the term "suitable" meant to modify the scope of binding partners to encompass only those that result in a diffraction-quality co-crystal with TACE? While claim 7 limits the binding partner to a "hydroxamate-based binding partner," it remains unclear, even among those binding partners that are considered to be "hydroxamate-based" as to those that are "suitable" or not for co-crystallization. It is suggested that applicant clarify the meaning of the claim.

[d] Claims 11-12 recite the limitation "TCD molecules." There is insufficient antecedent basis for this limitation in the claims. In view of claim 2, it appears that applicant's intended meaning of "TCD" is TACE catalytic domain. However, as with claim 2, it is unclear as to those amino acids of a TACE catalytic domain that are intended as being encompassed by the claims. It is suggested that applicant clarify the meanings of the terms "TCD molecules."

[e] Claim 14 is unclear in the recitation of "characterized by" and "substantial part thereof." Regarding the phrase "characterized by," it is unclear as to whether the term is meant to be interpreted as meaning "has," or whether the term is meant to interpreted as the structure coordinates of Table 1 are merely representative or exemplary. Also, it is unclear as to the structural coordinates of Table 1 that are considered to be a

"substantial part thereof" and whether these structural coordinates are required to be structural coordinates of a contiguous set of amino acids or selected amino acids. It is suggested that applicant clarify the meanings of the terms "characterized by" and "substantial part thereof."

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[13] Claim(s) 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-14 and 22 are drawn to a composition comprising a genus of TACE polypeptides in crystalline form, optionally in a co-crystal with a genus of binding partners. Claims 15-21 are drawn to a method for crystallizing a genus of TACE polypeptides and a genus of binding partners in a genus of crystallization buffers.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical

and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single species of the genus of recited or claimed TACE polypeptides used in crystallization, *i.e.,* TACE as disclosed in Black et al., "A Metalloproteinase disintigrin that releases tumour-necrosis factor-.alpha. from cells," Nature 385: 729-733 (February 1997), with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells. Specification at p. 31. The specification discloses only a single species of the genus of TACE crystals and binding partners thereof, *i.e.,* a crystal of the purified TACE polypeptide described above co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m-ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41°. Also, the specification discloses only a single representative species of crystallization buffers that resulted in a TACE crystal that was suitable for x-ray diffraction, *i.e.,* 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol. The specification fails to disclose any other representative species of the genus of TACE crystals, TACE proteins, and TACE binding partners and also fails to disclose any other representative

species of crystallization buffers that can be used to achieve a diffraction-quality crystal. Other than these single representative species, the specification fails to disclose any additional species of the genus of compositions, TACE proteins, TACE binding partners, and crystallization buffers, which encompass widely variant species. The genus of compositions encompasses TACE protein crystals of any TACE polypeptide, optionally liganded with any binding partner, having any space group and unit cell dimensions. The genus of TACE polypeptides encompasses any TACE polypeptide having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides. The genus of TACE binding partners encompasses any protein, antibody, or small molecule inhibitor that binds to a TACE polypeptide. The genus of crystallization buffers encompasses a buffer having any composition. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus".

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[14] Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of a purified TACE protein as disclosed

in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol, does not reasonably provide enablement for all crystals, TACE polypeptides, TACE binding partners, and methods of crystallization as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1-14 and 22 are so broad as to encompass crystals of any TACE polypeptide, having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides, optionally liganded with any binding partner having any structure, having any space group and unit cell dimensions. Claims 15-21 are so broad as to encompass a method for crystallizing a TACE polypeptide using any TACE polypeptide, having any sequence of amino acids, including any mutant and variant TACE polypeptides, including non-functional TACE polypeptides, liganded with any binding partner, under any crystallization conditions. The broad scope of claimed crystals and crystallization methods is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal with an expectation that the crystal will be of diffraction quality. The reference of Branden et al. ("Introduction to Protein Structure

Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). In view of these teachings, there is no expectation that a skilled artisan can use the disclosed crystallization conditions to achieve diffraction quality crystals of other TACE polypeptides. Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other TACE polypeptides optionally having a desired space group and unit cell dimensions as

encompassed by the claims can be achieved using *any* crystallization parameters as encompassed by the claims. Further, it is noted that the asserted utility of the claimed crystal is for determination of the structure of TACE for structure based design of TACE inhibitors (p. 2, first full paragraph), and it is highly unpredictable as to whether mutant and variant TACE polypeptides will maintain a three-dimensional structure that is equivalent to wild-type TACE for design of biologically relevant TACE inhibitors.

The amount of direction provided by the inventor; The existence of working examples: As noted above, the specification discloses the utility of the claimed crystal is in the determination of the 3-D structure of TACE (p. 2, first full paragraph), which, as acknowledged by Branden et al. at p. 374, requires a diffraction-quality crystal. In this case, the specification discloses only a single working example of such a diffraction quality crystal and method of making thereof, *i.e.,* a crystal of a purified TACE protein as disclosed in Black et al. (*supra*) with Ser266 changed to Ala, Asn452 changed to Gln and the sequence Gly-Ser-$(His)_6$ added to the C-terminus, and expressed in CHO cells, co-crystallized with N-[D,L-[2-(hydroxyaminocarnbonyl)m- ethyl]-4-methyl-pentanoyl)-L-3-(tert-butyl)-glycyl-L-alanine, having monoclinic space group $P2_1$ and the unit cell dimensions a = 61.38 Å, b=126.27 Å, c=81.27 Å, β=107.41° produced according to the method set forth in the specification at pp. 33-34 in the crystallization buffer 0.1 M sodium citrate, pH 5.4, 20 % w/v PEG 4000, and 20% v/v isopropanol. Other than this single working example of a crystal and method for making, the specification fails to provide guidance for crystallizing other polypeptides as encompassed by the claims with an expectation of obtaining diffraction-quality crystals optionally having the recited

space group and/or unit cell dimensions. It should be noted that the claims encompass crystals of mutant and variant TACE polypeptides and the specification fails to provide guidance for using those crystals that do not represent biologically relevant TACE polypeptides.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, it was not routine in the art to screen all polypeptides having a substantial number of variations and modifications as encompassed by the claims for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims and to determine those polypeptide structures that represent biologically-relevant TACE structures. Also, while methods of generating variants of a given polypeptide were known, *e.g.*, mutagenesis and hybridization, it was not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications, as encompassed by the instant claims. Further, while methods of assaying for binding partners were known in the art at the time of the invention, it was not routine to screen for any and all binding partners of a given protein.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystal and polypeptide compositions as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to

enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[15] Status of the claims:

Claims 1-27 are pending.

Claims 23-27 are withdrawn from further consideration.

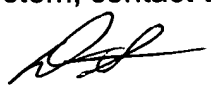
Claims 1-22 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.

Primary Examiner
Art Unit 1656